REMARKS

The allowance of claim 22 is acknowledged. The remaining claims were rejected under 35 U.S.C. § 103 based upon some new prior art.

Claims 2 and 21 have been canceled and claims 1 and 20 are amended to include subject matter therefrom. Claims 3-5 and 9-11 have been amended to now depend from allowed claim 22.

It is submitted that independent claims 1 and 20 would not be obvious based upon the combination of U.S. Patent Publication No. 2003/0054386 to Antonarakis et al (hereinafter Antonarakis) in view of the Markoulatos et al article in J. Clin. Lab. Anal. 2002; 16(1):47-51 (hereinafter Markoulatos) and U.S. Patent No. 6,040,138 to Lockhart et al (hereinafter Lockhart), and further in view of U.S. Patent No. 6,251,601 to Bao et al (hereinafter Bao).

The primary reference to Antonarakis describes a highly quantitative method of screening for one particular chromosomal abnormality at a time; it is premised upon the ability to search for and find highly similar, unique stretches of nucleic acids on two different genes. These similar nucleic acid sequences on different chromosomes need to have greater than 80% identity and be of substantially the same length; they must also be able to be amplified by PCR using a single pair of primers. The rationale behind the Antonarakis invention is set forth in paragraph 94 on page 10 where it is said that the rationale for using paralogous genes is that, since they are of almost identical size and sequence composition, they will PCR amplify with equal efficiency using a single pair of primers. Clearly, this is the sole focus of the procedure disclosed, and it is inconceivable that the teaching could be used to assay for more than one chromosomal aberration at a time because it is extremely unlikely that one will be able to locate highly similar, unique stretches of nucleic acids on three or more different genes of interest. The procedure is thus incapable of performing Applicants' claimed method of detection of any one of multiple chromosomal disorders in a single assay.

The Examiner remarks that "the concept behind the detection methods of Antonarakis and the instant invention are the same"; however, this is simply a truism.

One always is trying to determine whether deviations from a 1-to-1 ratio exist in order to determine if there is such a chromosomal abnormality. It is Applicants' overall method, including the ultimate analysis that constitutes the invention, not the mere fundamental concept.

Antonarakis is restricted to assaying for differences in a single chromosome at a time and to situations where it is able to locate similar unique nucleic acid structures that can be used for this purpose. In contrast, Applicants' described and claimed method is capable of detecting multiple chromosomal disorders on a variety of different chromosomes in a single assay, and of accomplishing such with reliable and reproducible results.

The Examiner cites Markoulatos for merely a disclosure of multiplex PCR; however, there is nothing in Markoulatos that would in any way suggest its use in assaying for multiple chromosomal abnormalities. Regardless of the availability of the Markoulatos procedure, one employing the highly similar, unique gene method of Antonarakis would have no use for such procedure.

The Examiner cites Lockhart as a disclosure that microarray technology was generally known (which of course it was) and for its mention of the GAPDH gene as a housekeeping gene that might be used as an expression level control in the gene expression assays of interest to Lockhart. However, Lockhart is deficient in any suggestion of Applicants' analysis set forth in step (g) that produces reliable results in diagnosing for multiple chromosomal disorders in a single assay using the recited overall method and the results obtained from the microarrays. Lockhart's concern involved the use of a corresponding mismatch probe for each probe of interest (see column 27, lines 42-58) which simply eliminated some members of the expression analysis being carried out.

Bao uses a microarray to carry out co-hybridization of nucleic acids from three or four different nucleic acid populations; each population is labeled with a different fluorescent color. Bao is not focusing on specific chromosomal nucleic acid stretches of interest through the use of multiple different pairs of primers wherein one control gene is

included. Instead, Bao uses entire genomic DNA or messenger RNA populations from tissue being analyzed and from normal tissue. Bao requires three or four entire populations of fluorescent-labeled nucleic acids for each assay, and then must analyze each of the target element spots on the microarray for four different fluorescent readings, correct for background from different fluorescent singles on the same spot, and then compare the relevant signals from that one spot. This is in direct contrast to Applicants, who create only a single set of fluorescent-labeled single strand products for each assay, and employ a control gene in the form of a chromosome that is not subject to duplication; the result is a greatly simplified procedure where reliable assaying for multiple chromosomal disorders is achieved in a single procedure using the recited ultimate analysis. Applicants' method is effective and reliable because of the analysis that is carried out using the laboratory test results through the use of adjustment via C-factors and an average C-factor.

In summary, Antonarakis can assay for only a single chromosomal disorder in one procedure. Markoulatos simply teaches fine-tuning multiplex PCR with an eye toward overcoming previous problems with respect to sensitivity and preferential amplification. It does no more than indicate that this is a tool that is available for laboratory usage. Lockhart fine-tunes microarray expression analyses by using a mismatch probe for each probe. Bao merely discloses the use of PCR if the available nucleic acid population is felt to be insufficient: "If less than about one million cells are available, a nucleic acid amplification or concentration is preferably used. Preferably, such an amplification technique is PCR." (column 12, lines 24-26). It is not an integral part of the Bao procedure. Bao does not use a plurality of different pairs of forward and reverse DNA primers to produce labeled, single-stranded DNA products. Most importantly, the Bao procedure is not based upon obtaining intensities from the imaging of different spots on a microarray with respect to one chromosome of interest and with respect to a single control gene and then making a reliable diagnosis using the recited analysis procedure. Bao does not use a control gene, but for each assay includes an entire population of nucleic acid for similar normal tissue and then obtains a spot which when imaged shows

three or four different colorimetric intensities that need to be differentiated. Bao's only adjustment is for background.

It is submitted that, in fairness, without prior knowledge of Applicants' disclosure, one would not think of making such radical changes to either the procedure of Antonarakis or the procedure of Bao to achieve a reliable analysis of multiple chromosomal disorders through the use of a single control gene and the recited analysis of Applicant's step (g) when neither of the references is concerned with solving such a problem.

In view of the foregoing, reconsideration of the rejection under Section 103 in view of amended claims 1 and 20 and withdrawal of it are respectfully requested. It is submitted that claims 1, 8 and 20 should now be allowed, along with allowed claim 22 and claims 3-7 and 9-11 which are dependent thereupon. It is believed that the application has been placed in condition for allowance and favorable action is courteously solicited.

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Respectfully submitted,

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